REMARKS

Applicants respectfully request reconsideration. Claims 52-53, 55, and 60-61 were previously pending in this application. By this amendment, claims 52 and 61 are being amended. As a result, claims 52-53, 55, and 60-61 now are pending for examination with claim 52 being an independent claim. No new matter has been added.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 52-53, 55, and 60-61

Claims 52-53, 55, and 60-61 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirements as the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree with these assertions by the Examiner.

In re Wands Factors

As MPEP § 2164.01(a) states, to determine whether there is sufficient evidence to support a finding that a disclosure does not satisfy the enablement requirement, the In re Wands 858 F.2d 737, 8 USPQ2d 1400 (Fed. Cir. 1988) factors (the "Wand's Factors") are weighed. The Wand's factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Each of these factors will be addressed in turn.

(1) The claims are not overly broad. Independent claim 52 has been amended to further clarify the claimed invention. As amended, independent claim 52 is directed to a method of delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotype response directed against said antibody in said mammal, said method including, *inter alia*, transplanting a genetically modified mammal cell which includes a polynucleotide including, *inter alia*, a nucleotide sequence encoding an antibody or fragment thereof to be delivered; a promoter sequence controlling expression of the nucleotide sequence in the cell; and an element guaranteeing the secretion of the encoded antibody or fragment thereof; wherein said polynucleotide is expressed and the cell secretes the encoded antibody or fragment thereof such that the antibody or fragment thereof reaches the blood circulation of the subject mammal; wherein said cell is a cell not specialized for the production of antibodies, which has the ability (a) to secrete proteins, (b) to live in the mammal subject, and wherein said cell derives from the subject mammal or from another mammal, which is a compatible donor; and wherein an anti-idiotypic response is not triggered. As will be discussed further below, these amendments further narrow the claimed invention.

(2) and (3) The nature of the invention and the state of the prior art at the time the invention was filed demonstrate that the level of knowledge in the art would not have required undue experimentation to make or use the claimed invention. All techniques, methods, and procedures employed in making and/or using the claimed invention were known and used at the time of the invention. For example, gene transfer techniques, such as those based on classical murine retroviruses cell grafting methods, such as the grafting of cultured and primary myogenic cells, and analysis procedures, such as antibody concentration assays using ELISA, were all routinely used in laboratories at the time of the invention. Therefore, the nature of the invention would not have required undue experimentation for one skilled in the art to make and/or use the claimed invention, specifically when the state of the art pertaining to the treatment of disease by antibody mediated gene/cell therapy was developed.

(4) Persons skilled in the art at the time the application was filed would have been able to carry out the aspect of the invention applicable to their specialty without undue experimentation. Additional evidence of this is stated above with regard to elements (2) and (3).

(5) The state of the art with respect to antibody-mediated gene/cell therapy was not unpredictable at the time the invention was filed. The Examiner relies on Qu et al. (The Journal of Cell Biology, 142: 1257-1267, 1998) to assert that myogenic cells that have been grafted onto mice do not survive in the long term and therefore there is no indication that they are therapeutically effective. While the art of allogenic or xenogenic anti-body gene/cell therapy has not been tested before and a large number of myogenic cells are lost through procedures such as purification or grafting, it is important to underline that a fraction of cells survive, and that the latter cells both survive in the long-term and can contribute to the formation of functional muscle fibers. In fact, Qu et al. does not address the cells that survive in the long-term but reports on the facts that several closely related cell populations are found in primary myoblast cultures (as evidenced using a series of biomarkers) and that some of these populations, but not all of them, disappear rapidly after grafting to syngenic animals. Therefore, Qu et al. is not relevant to determining the predictability or unpredictability of the state of the art of antibody-mediated gene/cell therapy.

Additional support for the assertion that the state of the art with respect to antibody-mediated gene/cell therapy was not unpredictable at the time the invention was filed can be found in the prior art. For example, Noël et al. (Journal of Investigative Dermatology 115: 740-745, 2000) teaches that no anti-idiotypic response could be detected when an immunocompetent mouse is transplanted with genetically engineered fibroblastic cells producing a recombinant antibody that is released in the blood. In this sense, the prior art provides guidance for producing an antibody using standard expression systems that are sufficient for not inducing any adverse anti-idiotypic response in the treated subject. The present invention is directed to a method of delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotype response and is thus predictable in light of prior art.

(6) Furthermore, the Applicants have provided guidance for overcoming an anti-idiotypic response against a recombinant antibody produced at an ectopic site in vivo. As stated above, standard gene/cell transfer techniques, which do not induce an inflammatory response, are sufficient to enable the delivery of an antibody or fragment thereof without triggering an anti-idiotypic response.

(7) The Examiner states that Applicants have failed to provide working examples that correlate to the treatment of a disease by antibody-mediated gene/cell therapy and that Applicants have not performed in vivo experiments of the produced recombinant antibody at the ectopic site to detect levels of anti-idiotypic response that are not detected by the sensitivity of the ELISA assay in vitro. Applicants respectfully disagree.

With regard to the Examiner's contention that Applicants have failed to provide working examples, M.P.E.P. §2164.02 states that "a single working example in the specification is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled," and that "the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors." To make a rejection based on a single working example, the Examiner would have to examine all the facts and evidence and state why "one would not expect to be able to extrapolate that one example across the entire scope of the claims." (M.P.E.P. §2164.02).

Applicants have provided at least two working examples in the specification. For example, in paragraphs [0090]-[0092] of the specification, Applicants describe an *in vivo* experiment where genetically modified cells were implanted into mice, resulting in an elevated production of recombinant antibodies. In paragraphs [0093]-[0097], Applicants describe another experiment where primary myogenic cells expressing monoclonal antibody were implanted into mice and no anti-idiotypic response was measured using ELISA. Applicants have provided at least two working examples and have thus met the burden under M.P.E.P. §2164.02.

With regard to the Examiner's contention that Applicants have not performed *in vivo* experiments aiming at detecting possible anti-idiotypic antibody production at the site of ectopic monoclonal antibody production, Applicants submit that this was not necessary. Such experiments are not technically feasible and are incompatible with the reality of the mounting of an immune response. There is no interest in measuring the concentration of anti-idiotypic antibodies at the site of production of the monoclonal antibody because anti-idiotypic antibodies are generated and produced at sites (namely, secondary lymphoid organs) that are distant from the grafting site of genetically modified cells. Furthermore, the local concentration of the ectopic monoclonal antibody at the site of its production is not greater than at any other places in the

body of the treated mammal due to both the inherent stability of antibodies and the fact that they are distributed throughout the body via the blood flow and the lymph within seconds to minutes after release from the producing cells. It is therefore not necessary for Applicants to perform the *in vivo* experiments the Examiner suggests.

(8) The quantity of experimentation necessary to carry out the claimed invention is reasonable. As stated above in regard to elements (2) and (3), all techniques, methods, and procedures employed in making and/or using the claimed invention were known and used at the time of the invention. Also, as stated above with regard to element (7), Applicants have provided working examples. In addition, all protocols and experimental procedures which may be used to perform the claimed method could be found in the literature at the time the application was filed.

In view of the foregoing, Applicants have complied with the enablement requirements as the claims contain subject matter, which was described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Support for Prior Amendments

The Examiner asserts that there is no support in the specification for the prior amendment to claim 52. Applicants respectfully disagree. For example, paragraphs [0039]-[0041] of the present specification provide support for the recitation that the non-antibody producing cells to have the ability (a) to secrete proteins in the blood circulation of a mammal and to live (b) a long life in the mammal's organism.

Clarification of Lack of Anti-Idiotypic Response Inducement

The Examiner asserts that Applicants support the notion that there could be an anti-idiotypic antibody response against a recombinant antibody produced *in vivo* at an ectopic site, which is confusing because the claims state without triggering such a response. Applicants respectfully disagree. There is no a contradiction by claiming an embodiment of the invention which does not trigger an anti-idiotypic response and using an article in which there could be an

anti-idiotypic response to show that the state of the art provides for conditions under which an anti-idiotypic response might be induced.

Specifically, Noël et al. (Journal of Investigative Dermatology 115: 740-745, 2000) teaches that no anti-idiotypic response could be detected when an immunocompetent mouse is transplanted with fibroblastic cells expressing antibodies; however, some anti-idiotypic response might be induced when there is direct *in vivo* transfer using very high doses of recombinant adenoviruses (see e.g., Noël et al., "A high in vivo monoclonal antibody production upon adenoviral gene transfer can induce a low but non neutralizing anti-idiotypic response," Human Gene Therapy, 13:1483-1493, 2002). Such conditions are very inflammatory and life-threatening to animals and thus, would never be used to treat human beings. Applicants were merely using Noël et al. to show that there are conditions, which are not applicable to the present invention, under which an anti-idiotypic response might be induced. The present claims are directed to a method of delivering an antibody or fragment thereof without triggering an anti-idiotypic response.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 52 and 61

Claims 52 and 61 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Without acceding to the propriety of the rejection, claims 52 and 61 have been amended to further define the claimed subject matter.

Claim 52

The Examiner asserts that claim 52 does not recite method steps which accomplish the recitation in the preamble that the method is practiced "without triggering an anti-idiotypic response."

As amended, independent claim 52 is directed to a method of delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotype response directed against said antibody in said mammal, said method including, *inter alia*, transplanting a genetically modified mammal cell which includes a polynucleotide including, *inter alia*, a

nucleotide sequence encoding an antibody or fragment thereof to be delivered; a promoter sequence controlling expression of the nucleotide sequence in the cell; and an element guaranteeing the secretion of the encoded antibody or fragment thereof; wherein said polynucleotide is expressed and the cell secretes the encoded antibody or fragment thereof such that the antibody or fragment thereof reaches the blood circulation of the subject mammal; wherein said cell is a cell not specialized for the production of antibodies , which has the ability (a) to secrete proteins, (b) to live in the mammal subject, and wherein said cell derives from the subject mammal or from another mammal, which is a compatible donor; and wherein an anti-idiotypic response is not triggered. Support for this amendment may be found, for example, in paragraph [0097] of the specification.

The Examiner states that functional language renders the claim improper. Applicants respectfully disagree.

Functional language does not render a claim improper (In re Swinehart, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)). According to M.P.E.P. § 2173.05(g), "a functional limitation is often used in association with an element, ingredient or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step." Additionally, In re Barr, 444 F.2d 588, 170 USPQ 33 (CCPA 1971) held that "the limitation used to define a radical on a chemical compound as 'incapable of forming a dye with said oxidizing developing agent' although function, was perfectly acceptable because it set definite boundaries on the patent protection sought". In the present case, the recitation of "not triggering an anti-idiotype response" is very similar to the "incapable of forming a dye" recitation of In re Barr and should be "perfectly acceptable" for at least the same reasoning. Therefore, the recitation of claim 52 "wherein an anti-idiotypic response is not triggered" does not render claim 52, or any of its dependent claims, improper.

In view of the foregoing, independent claim 52 distinctly claims the subject matter, and withdrawal of the rejection under §112 is respectfully requested.

Claim 61

The Examiner asserts that claim 61 is vague and incomplete in the recitation of "therapeutically effective" because the therapy that is encompassed or to be affected by the

general method of delivery set forth in claim 52 is not clearly set forth. As suggested by the Examiner, claim 61 has been amended to define the "antibody" as a "therapeutic antibody."

As amended, dependent claim 61 is directed to a method for delivering an antibody or a fragment thereof to a subject mammal wherein, *inter alia*, the antibody or fragment thereof reaching the blood circulation of a mammal subject is a therapeutic antibody or fragment thereof and is present in a quantity which is therapeutically effective.

In view of the foregoing, dependent claim 61 distinctly claims the subject matter, and withdrawal of the rejection under §112 is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims clearly and distinctly set forth the subject matter of the present invention.

Accordingly, Applicants submit that the claims are now in condition for allowance. Withdrawal of the pending rejections, and early and favorable reconsideration are respectfully solicited. In the event that a telephone conversation would further prosecute and/or expedite allowance, the Examiner is invited to contact the undersigned at (617) 310-6000.

Respectfully submitted,

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